Exhibit 5

Reference Manual on Scientific Evidence

Third Edition

Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence

Committee on Science, Technology, and Law
Policy and Global Affairs

FEDERAL JUDICIAL CENTER

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no effort. Fundamentally, the task is an inferential process of weighing evidence and using judgment to conclude whether or not an effect is the result of some stimulus. Judgment is required even when using sophisticated statistical methods. Such methods can provide powerful evidence of associations between variables, but they cannot prove that a causal relationship exists. Theories of causation (evolution, for example) lose their designation as theories only if the scientific community has rejected alternative theories and accepted the causal relationship as fact. Elements that are often considered in helping to establish a causal relationship include predisposing factors, proximity of a stimulus to its putative outcome, the strength of the stimulus, and the strength of the events in a causal chain. Unfortunately, judges may be in a less favorable position than scientists to make causal assessments. Scientists may delay their decision while they or others gather more data. Judges, on the other hand, must rule on causation based on existing information. Concepts of causation familiar to scientists (no matter what stripe) may not resonate with judges who are asked to rule on general causation (i.e., is a particular stimulus known to produce a particular reaction) or specific causation (i.e., did a particular stimulus cause a particular consequence in a specific instance). In the final analysis, a judge does not have the option of suspending judgment until more information is available, but must decide after considering the best available science. Finally, given the enormous amount of evidence to be interpreted, expert scientists from different (or even the same) disciplines may not agree on which data are the most relevant, which are the most reliable, and what conclusions about causation are appropriate to be derived.

Like causation, conflict of interest is an issue that cuts across most, if not all, scientific disciplines and could have been included in each chapter of the *Reference Manual*. Conflict of interest manifests as bias, and given the high stakes and adversarial nature of many courtroom proceedings, bias can have a major influence on evidence, testimony, and decisionmaking. Conflicts of interest take many forms and can be based on religious, social, political, or other personal convictions. The biases that these convictions can induce may range from serious to extreme, but these intrinsic influences and the biases they can induce are difficult to identify. Even individuals with such prejudices may not appreciate that they have them, nor may they realize that their interpretations of scientific issues may be biased by them. Because of these limitations, we consider here only financial conflicts of interest; such conflicts are discoverable. Nonetheless, even though financial conflicts can be identified, having such a conflict, even one involving huge sums of money, does not necessarily mean that a given individual will be biased. Having a financial relationship with a commercial entity produces a conflict of interest, but it does not inevitably evoke bias. In science, financial conflict of interest is often accompanied by disclosure of the relationship, leaving to the public the decision whether the interpretation might be tainted. Needless to say, such an assessment may be difficult. The problem is compounded in scientific publications by obscure ways in which the conflicts are reported and by a lack of disclosure of dollar amounts.

Reference Guide on Epidemiology

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D. Have the Results Been Replicated?

Rarely, if ever, does a single study persuasively demonstrate a cause–effect relationship.[162] It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists.[163]

The need to replicate research findings permeates most fields of science. In epidemiology, research findings often are replicated in different populations.[164] Consistency in these findings is an important factor in making a judgment about causation. Different studies that examine the same exposure–disease relationship generally should yield similar results. Although inconsistent results do not necessarily rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality.

E. Is the Association Biologically Plausible (Consistent with Existing Knowledge)?[165]

Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops. When biological plausibility exists, it lends credence to an inference of causality. For example, the conclusion that high cholesterol is a cause of coronary heart disease is plausible because cholesterol is found in atherosclerotic plaques. However, observations have been made in epidemiologic studies that were not biologically plausible at the time but subsequently were shown to be correct.[166] When an observation is inconsistent with current biological knowledge, it should not be discarded, but

162. In *Kehm v. Procter & Gamble Co.,* 580 F. Supp. 890, 901 (N.D. Iowa 1982), *aff'd,* 724 F.2d 613 (8th Cir. 1983), the court remarked on the persuasive power of multiple independent studies, each of which reached the same finding of an association between toxic shock syndrome and tampon use.

163. This may not be the legal standard, however. *Cf.* Smith v. Wyeth-Ayerst Labs. Co., 278 F. Supp. 2d 684, 710 n.55 (W.D.N.C. 2003) (observing that replication is difficult to establish when there is only one study that has been performed at the time of trial).

164. *See* Cadarian v. Merrell Dow Pharms., Inc., 745 F. Supp. 409, 412 (E.D. Mich. 1989) (holding a study on Bendectin insufficient to support an expert's opinion, because "the study's authors themselves concluded that the results could not be interpreted without independent confirmatory evidence").

165. A number of courts have adverted to this criterion in the course of their discussions of causation in toxic substances cases. *E.g., In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1247–48 (W.D. Wash. 2003); Cook v. United States, 545 F. Supp. 306, 314–15 (N.D. Cal. 1982) (discussing biological implausibility of a two-peak increase of disease when plotted against time); Landrigan v. Celotex Corp., 605 A.2d 1079, 1085–86 (N.J. 1992) (discussing the existence vel non of biological plausibility); *see also* Bernard D. Goldstein & Mary Sue Henifin, Reference Guide on Toxicology, Section III.E, in this manual.

166. *See In re* Rezulin Prods. Liab. Litig., 369 F. Supp. 2d 398, 405 (S.D.N.Y. 2005); *In re* Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003).

the observation should be confirmed before significance is attached to it. The saliency of this factor varies depending on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works. The mechanisms of some diseases are understood quite well based on the available evidence, including from toxicologic research, whereas other mechanism explanations are merely hypothesized—although hypotheses are sometimes accepted under this factor.[167]

F. Have Alternative Explanations Been Considered?

The importance of considering the possibility of bias and confounding and ruling out the possibilities is discussed above.[168]

G. What Is the Effect of Ceasing Exposure?

If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with cigarette smoking and lung cancer. In many situations, however, relevant data are simply not available regarding the possible effects of ending the exposure. But when such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.

H. Does the Association Exhibit Specificity?

An association exhibits specificity if the exposure is associated only with a single disease or type of disease.[169] The vast majority of agents do not cause a wide vari-

167. *See* Douglas L. Weed & Stephen D. Hursting, *Biologic Plausibility in Causal Inference: Current Methods and Practice,* 147 Am. J. Epidemiology 415 (1998) (examining use of this criterion in contemporary epidemiologic research and distinguishing between alternative explanations of what constitutes biological plausibility, ranging from mere hypotheses to "sufficient evidence to show how the factor influences a known disease mechanism").

168. *See supra* Sections IV.B–C.

169. This criterion reflects the fact that although an agent causes one disease, it does not necessarily cause other diseases. *See, e.g.,* Nelson v. Am. Sterilizer Co., 566 N.W.2d 671, 676–77 (Mich. Ct. App. 1997) (affirming dismissal of plaintiff's claims that chemical exposure caused her liver disorder, but recognizing that evidence supported claims for neuropathy and other illnesses); Sanderson v. Int'l Flavors & Fragrances, Inc., 950 F. Supp. 981, 996–98 (C.D. Cal. 1996); *see also* Taylor v. Airco, Inc., 494 F. Supp. 2d 21, 27 (D. Mass. 2007) (holding that plaintiff's expert could testify to causal relationship between vinyl chloride and one type of liver cancer for which there was only modest support given strong causal evidence for vinyl chloride and another type of liver cancer).

When a party claims that evidence of a causal relationship between an agent and one disease is relevant to whether the agent caused another disease, courts have required the party to show that